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REVIEW

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LONG-TERM EXPOSURE TO MICROWAVE RADIATION PROVOKES CANCER GROWTH: EVIDENCES FROM RADARS AND MOBILE COMMUNICATION SYSTEMS

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In this review we discuss alarming epidemiological and experimental data on possible carcinogenic effects of long term exposure to low intensity microwave (MW) radiation. Recently, a number of reports revealed that under certain conditions the irradiation by low intensity MW can substantially induce cancer progression in humans and in animal models. The carcinogenic effect of MW irradiation is typically manifested after long term (up to 10 years and more) exposure. Nevertheless, even a year of operation of a powerful base transmitting station for mobile communication reportedly resulted in a dramatic increase of cancer incidence among population living nearby. In addition, model studies in rodents unveiled a significant increase in carcinogenesis after 17-24 months of MW exposure both in tumor-prone and intact animals. To that, such metabolic changes, as overproduction of reactive oxygen species, 8-hydroxi-2-deoxyguanosine formation, or ornithine decarboxylase activation under exposure to low intensity MW confirm a stress impact of this factor on living cells. We also address the issue of standards for assessment of biological effects of irradiation. It is now becoming increasingly evident that assessment of biological effects of non-ionizing radiation based on physical (thermal) approach used in recommendations of current regulatory bodies, including the International Commission on Non-Ionizing Radiation Protection (ICNIRP) Guidelines, requires urgent reevaluation. We conclude that recent data strongly point to the need for re-elaboration of the current safety limits for non-ionizing radiation using recently obtained knowledge. We also emphasize that the everyday exposure of both occupational and general public to MW radiation should be regulated based on a precautionary principles which imply maximum restriction of excessive exposure.

***Key Words*: non-ionizing radiation, radiofrequency, tumor, risk assessment, safety limits, precautionary principle.**

INTRODUCTION

Electromagnetic radiation (EMR) became one of the most significant and fastest growing environmental factors due to intensive development of communication technologies during the last decades. Currently, according to expert estimations, the level of electromagnetic radiation from artificial sources exceeds the level of natural electromagnetic fields by thousand folds. The active development of mobile communication technologies over the world will only raise this level further. In this connection the problem of possible adverse effects of anthropogenic EMR on human health and particularly strictest assessment of possible carcinogenic effects of EMR is extremely important.

In August 2007 an international working group of renowned scientists and public health experts released a report on electromagnetic fields (EMF) and human health [1]. It raised a serious concern about safety limits for public electromagnetic irradiation from power lines, cell phones, radars, and other sources of EMF exposure in daily life. The authors concluded that the existing public safety limits were inadequate to protect public health. Moreover, very recently a vast number of new extremely important studies in this field have been published. Importantly, nowadays the problem is discussed on highest political level over the world. It appears that the most sound political document in Europe is a European Parliament Resolution from April 2, 2009 (*www.europarl.europa.eu*), where the direct appeals to activate the research and business strategy for effective solving of the problem over the member states were indicated.

In this review we would like to analyze the results of studies on specific biological effects of microwaves (MW), both epidemiological and experimental that deal with cancer promotion by long term low intensity microwave irradiation of human/animal beings. We will concentrate on unequivocal studies and will not analyze ambiguous data. For additional analysis of microwave risks we can recommend recently published reviews [2–10].

MICROWAVES OF RADARS AND MOBILE COMMUNICATION SYSTEMS

Microwaves are non-ionizing electromagnetic radiation. That means MW is a type of electromagnetic radiation which does not carry enough energy

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Abbreviations used: 8-OH-dG — 8-hydroxi-2-deoxyguanosine; EGF — epidermal growth factor; EMF — electromagnetic field; EMR — electromagnetic radiation; ERK — extracellular-signal-regulated kinase; GSM — Global System for Mobile communication; ICNIRP — International Commission on Non-Ionizing Radiation Protection; MW — microwaves; NHL — Non-Hodgkin lymphoma; ODC — ornithine decarboxylase; OER — observed expected ratio; OR — odds ratio; ROS — reactive oxygen species; SAR — specific absorption rate; SIR — standardized incidence ratio; SMR — standardized mortality ratio; WHO — the World Health Organization.

for ionization of atoms and molecules under normal conditions and unlike the ionizing radiation this kind of radiation generally has not enough energy for breaking the intermolecular bonds or for breakaway of electrons from atoms or molecules. MW comprise a part of radiofrequency range. Radiofrequency radiation (RF) refers to electromagnetic waves with a rate of oscillation of electromagnetic fields in the range from 30 kHz to 300 GHz. As any other electromagnetic waves, the radio waves are pulses of electric and magnetic fields. These fields regenerate each other as they move through the space at the speed of light. MW have frequencies from 300 MHz to 300 GHz. As MW have the highest frequency among other RF, it carries the highest energy and produce most thermal effect upon interaction with the matter.

The main sources of radiofrequency radiation during a long period in previous century were broadcasting systems. In some cases, for example, in military and aviation the most powerful local sources of radiofrequency radiation were and still are radars (RAdio Detection And Ranging). However, the situation changed dramatically for general population during recent decades; and currently the most prevailing sources of RF in nearest human environment are mobile communication systems. It is important that both radars and systems for mobile communication use the same microwave part of radiofrequency spectrum.

Radar systems are type of powerful sources of pulsed MW which generally effect only certain groups of military or service staff or population living nearby. Radars are detection systems which use MW to determine both moving and fixed objects like aircraft, ships, missiles, etc. Depending on the tasks they use different frequencies of MW, from 1GHz to 12 GHz.

Mobile communication systems are undoubtedly the most source of MW in human environment over the world nowadays. Starting from the first commercial mobile phone networks in Japan, Europe and USA since 1979–1983 the number of active users of mobile telephony increased globally to over five billion. In developed countries the number of cellular phone users today is over the point of saturation. It means that many people use more than one cell phone. The initial age of youngest users of cell phone is estimated as three years old [5].

Mobile communication technology utilizes MW for connection of cell phones and base transmitting stations. Phone refers to as mobile because it is free from wire connection and it refers to as cellular/cell because technology utilizes cellular network principle. All area is covered by many base transmitting stations, each station operates in one cell (part of area) and cell phone automatically changes the station when moves from one cell to another. In GSM (Global System for Mobile communication) standard, which covers about 80% of all services over the world the frequencies of electromagnetic waves used are about 850; 900; 1850; or 1900 MHz, which belongs to the microwave range. The useful information (sounds or images) is transferred by modulation of electromagnetic wave frequency. In GSM standard TDMA (Time Division Multiple Access) principle is realized. This means a part-time access of each consumer to the logical channel with frequency of channel rotation about 217 Hz. Thus, both base transmitting stations and cell phones emit MW modulated according to the digital standard.

SAFETY LIMITS FOR MICROWAVE RADIATION

The main international recommendations on safety levels of non-ionizing electromagnetic radiation is *Guidelines for Limiting Exposure to Time-Varying Electric, Magnetic, and Electromagnetic Fields (up to 300 GHz)* of International Commission on Non-Ionizing Radiation Protection [11]. The document gives recommended safety limits in all ranges of EMR both for occupational and general public exposure. "Basis for limitation exposure" is dramatically important for understanding the imperfection of this document. Accordingly, the document directly states that "Induction of cancer from long-term EMF exposure was not considered to be established, and so these guidelines are based on short-term, immediate health effects such as stimulation of peripheral nerves and muscles, shocks and burns caused by touching conducting objects, and elevated tissue temperatures resulting from absorption of energy during exposure to EMF." However, the basic assumption of that is questioned nowadays by numerous data sources.

According to that document a few parameters of EMR energy are recommended to be restricted. Among them the two parameters are used the most often: 1) Specific Absorption Rate (SAR) in W/kg, which indicates the EMR energy absorbed per mass unit of human tissue per second; and 2) power density or intensity of incident radiation in W/m^2 (or $\mu W/cm^2$) which indicates the amount of electromagnetic energy which falls on a unit of surface (under the right angle) per second. SAR safety limit for general public exposure indicated in Guidelines as 2 W/kg (for head and trunk) for the microwave range. To that, this limit is accepted by industry as mandatory for every commercial cell phone over the world, and real value of SAR of each cell phone model must be indicated in technical specification of the model. Unfortunately, SAR is rather sophisticated index for measurement. Moreover, only models of adult human head are currently used by industry for calculation of SAR, while real SAR values depend on a geometry and structure of tissues and, for example, was shown to be much higher for a child head than for the adult one [12–14].

Power density, or intensity of radiation, is much more direct and simple index as compared to SAR, although it does not estimate the specificity of interaction of EMR and the matter. Occupational exposure limits in microwave range according to ICNIRP are 10–50 W/m^2. Public exposure limits for microwaves according to ICNIRP recommendation were set to 2–10 W/m^2 (or 200–1000 $\mu W/cm^2$) depending on fre-

quency. For example, for GSM–900 MHz standard ICNIRP safety limit will be calculated as 450 μW/cm^2 [11].

It is important to note that ICNIRP recommendations have no legal validity, as it is only a recommendation. Each country has their own national legislation in the field of electromagnetic safety, and national limits are rather different in different countries. Some countries such as the USA and Germany conformed national EMR limits to ICNIRP recommendation. Other countries have much tougher national limits as compared with ICNIRP guidelines. For example, for GSM-900 MHz standard MW safety limits are: in Italy, Russia and China — 10 μW/cm^2, in Switzerland — 4 μW/cm^2, in Ukraine — 2.5 μW/cm^2 [1]. As we can see, some countries, including Ukraine, have extremely strict national safety limits. Such national positions are explained first of all by long-term national research traditions in a field of electromagnetic biology, and on experience in studying the non-thermal biological effects of this kind of radiation. On the other hand, some countries like Switzerland follow a strict precautionary principle (Better protect than sorry).

RADAR RADIATION AND CANCER PROMOTION

Substantial military and occupational data indicate a significant effect of pulse microwaves on cancer development and other pathological conditions in human. Accordingly, a statistically significant increase in immature red blood cells among workers exposed to a radar was reported [15]. In addition, radar-exposed workers had significantly lower levels of leukocytes and thrombocytes than workers distant from MW sources.

Among Polish soldiers (128 thousand personnel subjects aged from 20 to 59 years), soldiers of 20–29 years old exposed to radar microwaves during 1970–1979 had cancer incidence rates 5.5 folds higher than non-exposed soldiers [16]. The greatest rise of cancer cases was detected in blood-forming organs and lymphatic tissues: by 13.9 folds for chronic myelocytic leukemia and 8.6 folds for myeloblastic leukemia. The level of mortality among all exposed personnel was significantly higher than in unexposed: for colorectal cancer (observed-expected ratio, OER 3.2; 95 %), for cancer of esophagus and stomach (OER 3.2; 95 %), cancer of blood-forming system and lymphatic tissues (OER 6.3; 95 %) [17].

Almost two times more cases of cancer were indicated in the high-exposed American naval personnel served during the Korean War (1950–1954) as compared with the low-exposed subjects among 40 thousands of personnel [18]. Death rates for aviation electronic technicians, the group with the highest exposure rate, were significantly higher than those for the other personnel during the following years up to 1974 [15].

A very substantial increase in cancer incidence was also detected in commercial airline pilots. Thus, the standardized incidence ratio (SIR) for malignant melanoma cases was 10.2; 95.5 % for pilots of commercial airlines in Iceland [19]. Significantly increased risks of acute myeloid leukemia (SIR 5.1), skin cancer, excluding melanoma (SIR 3.0) and total cancer (SIR 1.2) were observed also among Danish male jet pilots [20]. These data have been explained as a result of excess cosmic ionizing radiation or even excessive sun radiation during a leisure time. However, analysis of brain cancers among US Air Force personnel has revealed that non-ionizing radiation and particularly MW had significant effect on cancer development (odds ratio, OR 1.38; 95%), whereas ionizing radiation had negative association with cancer cases (OR 0.58; 95 %) [21]. To that, standardizing mortality ratio (SMR) for brain tumors was 2.1; 95 % among German male cockpit crew members (6,017 people) [22]. Cancer risk was significantly raised (risk ratio 2.2; 95%) among cockpit crew members employed for 30 years as compared to those employed for less than 10 years. In addition, Non-Hodgkin's lymphoma (NHL) was also increased (SMR 4.2; 95%) among male cabin crew members (20,757 people). Importantly, any increase in cancers associated with ionizing (cosmic) radiation was not detected in this cohort study.

In another report, six incident cases of testicular cancer occurred within a cohort of 340 police officers between 1979 and 1991 in Seattle, Washington, observed/expected ratio was 6.9; $p<0.001$ [23]. Occupational use of hand-held radar was the only shared risk factor among all six officers, and all had a routine habit of keeping the radar gun directly in close proximity to their testicles. Similarly, in Ontario, Canada risk assessment among police officers exposed to radar devices for speed measurement (1,596 females and 20,601 males) revealed an increased risk among men for testicular cancer (SIR 1.3) and for melanoma (SIR 1.45; 95 %) [24].

In another study, eighty seven persons working with radars (and 150 matched control) were divided into risk groups according to frequencies of MW (200 KHz to 26 GHz) and power density (8 μW/cm^2 to 300 μW/cm^2) [15]. Three specific radiation cataracts in persons working with extremely high MW exposure were identified. Lens changes were associated with level of exposure in different risk groups.

Other occupational studies revealed the highest risk ratio (2.6) for acute myelogenous leukemia in radio and radar operators among all occupational groups studied [25]. In addition, excessive risk for breast cancer was detected (SIR 1.5) among Norwegian female radio and telegraph operators (2,619 women) with potential exposure to radio frequency (405 kHz — 25 MHz) [26].

RADIATION FROM MOBILE COMMUNICATION SYSTEMS AND CANCER PROMOTION

Cell phones. A significant increase of risk of particular brain tumors in long-term (10 years or more) users of cell phones and cordless phones has been detected in series of epidemiological studies of Swedish oncologist Prof. L. Hardell with colleagues [27–33].

It is important that for a short-term use of cell phones similar effects were absent or less evident [4].

The risk of development of high-grade glioma has increased in more than 3 times (OR 3.1; 95 %) for bilateral users of cell phones and in more than 5 times (OR 5.4; 95%) for ipsilateral users after 10 years of using [34].

The risk of development of acoustic neuroma for bilateral users of cell phones was OR 2.9; 95% and OR 3.5; 95 % for ipsilateral users after 10 years of using [29].

Notably, the highest risk of brain tumors has been detected in the youngest users of cell phones (20–29-yr) among all analyzed age groups (20–80 years old), with OR 5.91; 95% for ipsilateral use of cell phones. The highest risk was associated with more than 5-year using period in the 20–29-yr age group for analog cell phones (OR 8.17; 95%) [28].

International multiyear Interphone project conducted under the management of the World Health Organization and substantially supported by industry, was an interview-based case-control study with 2708 glioma and 2409 meningioma cases and matched controls, conducted in 13 countries using a common protocol [35]. The results of study were rather controversial. For example, authors were forced to declare "a reduced odds ratio related to ever having been a regular mobile phone users was seen for glioma (OR 0.81; 95 %) and meningioma (OR 0.79; 95 %), possibly reflecting participation bias or other methodological limitations." However, significantly increased risks of tumors development in "heavy" users of cell phones (with more than 1640 hours of using during less than four years) have been revealed in this study: for meningioma OR 4.8; 95 %, for glioma OR 3.77; 95% as compared with the matched controls [35]. One thousand and six hundred forty hours per four years means about one hour per day of a cell phone use. In this connection we can point to our data [36] that indicates amount of time which Ukrainian students (like students in other countries?) spend talking via cell phones every day. Our findings indicated that more than a half of them spend over one hour per day, and more than a quarter of them spend over two hours per day talking via cell phones every day.

Parotid gland, like a human brain, is another potential target for cell phone MW radiation during cell phone talks without hands-free devices. Thus, a study done by an Israeli team has indicated an association between a cell phone use and parotid gland tumors [37]. This study comprised 402 benign and 58 malignant cases of parotid gland tumors diagnosed in Israelis at age over 18 years in 2001–2003. The risk of parotid malignant tumors in intensive users of cell phones (for users with more than 5,479 hours of a use during less than five years) were OR 2.26; 95%. Recently new data have been published that totally a 4-fold increase of parotid malignant tumors in Israel during 1970–2006 took place, whereas other salivary glands tumors had been almost on a stable level during that period of time [38]. Previously, a Finnish study has revealed the OR 5.0; 95% for salivary gland cancer among all Finland digital cell phone subscribers compared with control population after one-two years of a cell phone use [39].

The odds ratio for Non-Hodgkin's lymphoma of T-cell, cutaneous and leukemia types has been found for analogue-cell-phone users as 3.4; 95%; for digital-phone users 6.1; 95 %; and for cordless-phone users 5.5; 95% by L. Hardell group [40]. An American study indicated OR 1.6; 95 % for NHL in users of cell phones with a period of use over eight years [41].

Uveal melanoma (in analysis of 118 cases with uveal melanoma and 475 controls in Germany) has been indicated to have odds ratio 4.2; 95% for people probable/certain exposed to cell phone radiation [42].

Testicular cancer (seminoma) risk had odds ratio 1.8; 95% for men keeping a cell phone during "stand by" in ipsilateral trousers pocket [43]. The results have been based on 542 cases of seminoma in Sweden.

Base transmitting stations. During the last decades more than one and half million base transmitting stations for mobile communication have been installed over the world. However, the World Health Organization suggested a priority to study effects mainly of cell phones, while discouraging studies on the effects of transmitting stations (with an exception of years 2003–2006 when WHO recommended studies of possible effects of radiation of transmitting stations as well) [44]. This is probably the main reason why only a few publications on this particular problem can be found to date [45–49].

The comparison of cancer cases among people living up to 400 m from base transmitting station and people living further than 400 m from station during 1994–2004 was carried out in Germany [48]. A total increase of cancer cases among people living nearby to transmitting station over the control population was 1.26 times during the first five-year period (1994–1998), and 3.11 times during the second five-year period (1999–2004) of operation of the station. Particularly, in the second period the increase of cancer cases was statistically significant both as compared with the population from more distant area and with the expected background incidence.

Population (n=622) living in the area nearby (up to 350 m) the cell phone base transmitting station (850 MHz, 1500 watt of full power) during one year of operation and matched individuals (n=1222) from other area have been compared In Israel [47]. There were 4.15 times more cases of cancer in transmitted station area than in the rest of a city. Relative cancer rates for females were 10.5 for close to station area, 0.6 for control area and 1 for the whole town. Cancer incidence of women in close to base station area was significantly higher ($p<0.0001$) as compared with the control area and the whole city. Keeping in mind that very significant increase in a number of cancer cases took place during only one year period, the authors of the study suggested that MW could provoke latent

cases of cancer in inhabitants of the area nearby transmitting station.

French and Spanish researchers also revealed that inhabitants living near base station for mobile communication (up to 300 m) developed significantly higher rates of many subjective symptoms of health like headache, fatigue, sleep disorder, depression as compared with the matched control from distant area [49, 50].

RODENT MODEL OF CANCER PROMOTION BY MICROWAVES

A highly representative research has been carried out at the University of Washington, Seattle commissioned by US Air Force [51]. The experimental rats (100 animals) were exposed during 24 months at 21.5 hours per day to 2,450-MHz pulsed microwaves at 800 pps with a 10 μs pulse width. The pulsed microwaves were square-wave modulated at 8 Hz. An average SAR was 0.4 W/kg for a 200-g rat. It was a model of long-term irradiation of Air Force pilots to pulsed microwaves of radar systems. Totally 155 indexes of metabolisms were checked out during the study. As a result, the most expressive effect of long-term MW irradiation of animals was a dramatic increase in a level of cancer cases. In total, 3.6 folds more cancer cases were detected in irradiated animals than in matched control. Lymphoma cases were diagnosed in the irradiated animals 4.5 times more often than in the control group. In addition, benign tumors of adrenal were detected seven folds more often in the irradiated animals than in the control.

In the next study under US Air Force contract, 200 female C3H/HeJ mice were exposed for 21 months (22 h/day, 7 days/week) to a horizontally polarized 435 MHz pulse-wave (1.0 ps pulse width, 1.0 kHz pulse rate) RF radiation environment with an incident power density of 1.0 mW/cm^2 (SAR 0.32 W/kg), while 200 mice were sham-exposed [52]. Although under the conditions of this study, an exposure of mice prone to mammary tumors did not affect the incidence of mammary tumors, when compared with the controls, some other tumor cases increased markedly. For example, bilateral cases of ovary epithelial stromal tumor raised by five folds; multiple cases of hepatocellular carcinoma, raised 3 folds, and adrenal gland tumor cases (total) raised 1.63 folds.

In the third published study of this series [53] the same prone-mammary tumor mice were irradiated during 20 months to continuous wave 2450 MHz MW radiation with SAR from 0.3 to 1 W/kg (20 h/day, 7 days/week). A hundred mice were exposed, while 100 mice were used as sham-exposed. As a result, the exposed mice had higher level of mammary tumors (1.27 folds), and higher total level of all types of tumor (1.38 folds) as compared with sham-exposed; the difference between groups was statistically insignificant. Meanwhile, multiple mammary tumor cases occurred in exposed mice twice more frequently than in sham exposed.

In other study mice with high incidence of spontaneous breast cancer and mice treated with 3,4-benzopyrene (BP) were irradiated to continuous wave 2,450 MHz microwaves in an anechoic chamber at 5 or 15 mW/cm^2 (2 hours daily, 6 sessions per week, 3 months) [54]. Irradiation with MW at either 5 or 15 mW/cm^2 resulted in acceleration of development of BP-induced skin cancer. Microwaves-exposed mice with high incidence of spontaneous breast cancer developed breast tumors earlier than control. Authors indicated that the promotion of cancer development and lowering of natural antineoplastic resistance was similar in mice exposed to MW at 5 mW/cm^2 and chronically stressed by confinement, but level of cancer cases in animals exposed to 15 mW/cm^2 was significantly higher as compared to chronically stressed by confinement control.

And in well-known study of M. Ripacholi *et al.* (1997) transgenic mice moderately predisposed to develop lymphoma spontaneously have been used for exposure to MW of 900 MHz, with pulse repetition frequency of 217 Hz, incident power densities of 2.6–13 W/m^2, and average SAR of 0.13–1.4 W/kg [55]. One group of mice (101 females) has been exposed for two 30-min periods per day during 18 months. Another group of mice (100 females) has been a sham-exposed control. Lymphoma risk was significantly higher, more than twice, in the exposed mice than in the matched control (OR 2.4; 95 %). In particular, follicular lymphoma was the major contributor to the increased tumor incidence.

MICROWAVES AND CELL METABOLISM

Free radical species, including reactive oxygen species (ROS), is an intrinsic feature of cell metabolism [56–58]. But disturbance of redox balance, uncontrolled activation of free radical processes, overproduction of ROS and/or suppression of antioxidant defense in cell often are the important signals of some hazardous changes in cell metabolism [59, 60]. That is why data indicated oxidative effect of some factor is extremely important in risk-assessment research.

A significant increase of ROS and nitrogen oxide generation in cells under non-thermal intensities of MW has been detected both *in vivo* [61–67] and *in vitro* [68–72]. Possibilities of mitochondrial and membrane NADH oxidase dependent ways of ROS generation in exposed cells have been suggested [71, 72]. Accordingly, it was found that the first step in MW (875 MHz, 0.07 mW/cm^2) interaction with model cells (Rat1 and HeLa) was mediated in the plasma membrane by NADH oxidase, which can rapidly (during the minutes) generate ROS [72]. ROS directly stimulate matrix metalloproteinases and allow them to cleave and release heparin-binding epidermal growth factor (EGF). This secreted factor activates the EGF receptor, which in turn activates the extracellular-signal-regulated kinase (ERK) cascade and thereby induces transcription and other cellular pathways. On the other hand, on the model of purified human

spermatozoa exposed to MW (1.8 GHz, SAR from 0.4 W/kg to 27.5 W/kg) a significant overproduction of ROS in mitochondria was detected, along with a significant reduction in motility and vitality of spermatozoa [71]. All observed effects were significantly correlated with SAR levels, suggesting that significant effects of MW exposure occurred under non-thermal levels of MW.

Therefore, MW can induce cellular oxidative stress, which in turn can cause cancer stimulation [57, 59]. To that, it is known nowadays that in addition to damage via oxidative stress, ROS in cells can play a role of a secondary messenger for certain intracellular signaling cascades which can induce oncogenic transformation [60].

DNA damage in cells exposed to low-intensive microwaves both *in vivo* and *in vitro* was demonstrated during the last years in more than 50 independent studies [73]. The most often method used for detection of DNA damage after the MW exposure was alkaline Comet Assay. A statistically significant increase of both single strand and/or double strand breaks of DNA has been detected in humans [74, 75], animal models [76–79] and cell cultures [76, 80–83] exposed to low intensity microwaves.

Recently, an oxygen damage of DNA in human spermatozoa through formation of 8-hydroxi-2-deoxyguanosine (8-OH-dG) under non-thermal microwaves irradiation *in vitro* has been demonstrated [71].

Consequently, as DNA mutation is a critical step in carcinogenesis and increased level of 8-OH-dG takes place in many tumors [60], the possibility of MW to initiate oxidative damage of DNA is extremely dangerous signal for risk-assessment studies.

Ornithine decarboxylase (ODC) significantly changes its activity under conditions of non-thermal microwave exposure [84–88]. It was one of the first markers of carcinogenesis revealed to be activated under the low intensity microwaves exposure. ODC is involved in processes of cell growth and differentiation, and its activity is raised in tumor cells. Although overexpression of ODC is not sufficient for transformation of normal cells into tumorigenic ones, an increased activity of the enzyme was shown to promote the development of tumors from pre-tumor cells [89].

DISCUSSION AND CONCLUSIONS

In this review we presented evidences for carcinogenic effects of low intensity microwaves. Both epidemiological and experimental data led us to a conclusion that at least under certain conditions the exposure to long term low intensity MW can lead to tumorigenesis. Supporting evidences come from statistically significant epidemiological data based either on long-term analysis, e.g., on mortality of US Navy personnel in 20 years after expose during the Korean War [15], or on relatively short, one year exposure, e.g., by base transmitting station for mobile communication in Israel [47]. In the latter case we fully agree with the authors that MW exposure most likely results in acceleration of pre-existed cancer development. It is of note here that the same conclusion was drawn in epidemiological research on fast increase cancer incidence among adult population in Colorado exposed to extremely low frequency radiation [90].

The main shortcoming of the most epidemiological data, both in military studies and in mobile communication risk assessment, is a lack of a strict dose measurement of exposure. We strongly suggest that in the forthcoming epidemiological studies the correct measurement of intensity and dosage of exposure should be obligatory. The example of a large-scale epidemiological research employing personal MW dosimeters can be found in recent studies in Germany [91–94]. On the other hand, we also realize that the levels of the MW exposure in contemporary epidemiological studies, at least in those which deal with mobile communication systems, were within the official "safety limits" set by appropriate national standards and ICNIRP recommendations. Therefore, taking into account the reviewed data, we conclude that the relatively long-term (e.g., 10 years) exposure to microwaves emitted from mobile communication devices operating within "safety limits" set by current regulating bodies can be considered as a potential factor for promotion of cancer growth. Indeed, in the most studies on rodents the intensity of MW exposure was appropriately measured, and in majority of them the MW intensity was below ICNIRP safety limits. Nevertheless, majority of these studies to a greater or lesser extent demonstrated obvious carcinogenic effects after long term exposure (up to 24 months). This further emphasizes that at least under certain conditions the exposure to both pulsed and continuous MW with intensities below the current official "safety limits" can indeed promote cancer development.

In addition, experimental evidences of involvement of typical markers of carcinogenesis like overproduction of reactive oxygen species or formation of 8-OH-dG under conditions of MW exposure further indicate potential danger of this type of radiation for human health. It is important to emphasize here that experimental data, especially obtained in studies *in vitro* often reveal significant biological effects even after short-term (e.g., only a few minutes) [72] and/or extremely weak intensity of exposure to MW (by several orders of magnitude lower than in ICNIRP recommendations) [95]. Taking these data into account we strongly suggest that currently used "thermal" assessment of potential hazards of MW exposure is far from being appropriate and safe.

Taken together, we state here that nowadays there is enough convincing data to appropriately assert that the long-term exposure to low intensity electromagnetic microwaves can indeed promote cancer development. To that, the official recommendations by ICNIRP and safety limits set by many national regulatory bodies for technical devices emitting microwave radiation, first of all for mobile communication systems, must be re-assessed according to the recent alarming

data; and additional studies for unprejudiced risk assessment must be carried out. At present, we strongly suggest for a wide implementation of precautionary principle for everyday microwave exposure that implies maximum restriction of excessive exposure.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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